TITLE OF THE INVENTION

Azabenzodiazepines as phosphodiesterase-4 inhibitors

FIELD OF THE INVENTION

The present invention relates to azabenzodiazepine compounds, to pharmaceutical compositions containing them, to their use as medicinal products and to process for preparing them. These compounds are useful for preparing medicinal products for treating complaints involving a therapy with a phosphodiesterase-4 (PDE4) inhibitor. These medicinal products are useful in particular for treating certain inflammatory conditions and allergic conditions and are more particularly useful in the treatment of various respiratory diseases such as asthma, emphysema and chronic bronchitis.

TECHNOLOGICAL BACKGROUND OF THE INVENTION

Cyclic adenosine 3',5'-monophosphate (cAMP) is a ubiquitous intracellular second messenger, which is intermediate between a first messenger (hormone, neurotransmitter or autacoid) and the cellular functional responses: the first messenger stimulates the enzyme responsible for the synthesis of cAMP; depending on the cells concerned, the cAMP then intervenes in a great number of functions: metabolic, contractile or secretory.

The effects of cAMP end when it is degraded by cyclic nucleotide phosphodiesterases, which are intracellular enzymes that catalyse its hydrolysis into inactive adenosine 5'-monophosphate.

At least 11 major families of cyclic nucleotide phosphodiesterases (PDE) have been distinguished in mammals, numbered from 1 to 11 according to their structure, their kinetic behaviour, their substrate specificity or their sensitivity to effectors (Beavo J.A. *et al.* (1990) Trends Pharmacol. Sci. 11, 150-155. Beavo J.A. *et al.* (1994) Molecular Pharmacol. 46, 399-405). The PDE4 enzymes are specific for cAMP.

Non-specific phosphodiesterase inhibitor compounds are known, which inhibit several families of enzymes. This is the case for certain methyl xanthines such as theophylline. These

compounds have a low therapeutic index, in particular on account of their action on types of PDE present in cells other than the target cells. Conversely, certain families of PDE can be selectively inhibited by various pharmacological agents : the hydrolysis of cyclic nucleotides is slowed down and their concentration thus increases in only the cells in which the type of PDE that is sensitive to the inhibitor is found.

A specific advantage is shown for the phosphodiesterases 4 (PDE4), which have been identified in many tissues including the central nervous system, the heart, vascular endothelium, vascular smooth muscle and that of the aerial pathways, myeloid lines and lymphoid lines.

An increase in cAMP in the cells involved in inflammation inhibits their activation: inhibition of the synthesis and release of mediators in mastocytes, monocytes, polymorphonuclear eosinophils and basophils, inhibition of chemotaxis and degranulation of polymorphonuclear neutrophils and eosinophils, inhibition of the proliferation and differentiation of lymphocytes.

Cytokines, in particular TNF and interleukins, produced by various types of leukocytes such as the T lymphocytes, monocytes and polymorphonuclear eosinophils, play an important role in triggering inflammatory manifestations, in particular in response to stimulation by an allergen in the respiratory pathways.

Moreover, cAMP reduces the tonus of the smooth muscle fibres in the aerial pathways.

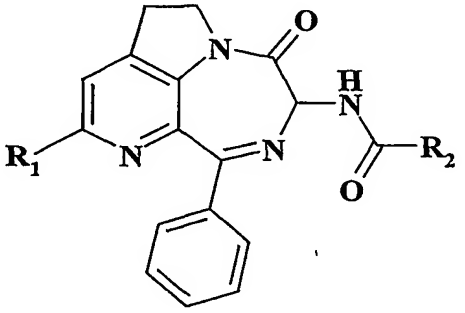
It might thus be expected that selective PDE4 inhibitors would have therapeutic activity as anti-inflammatory and anti-allergic medicinal products, and in the treatment of various respiratory diseases such as asthma, emphysema and chronic bronchitis.

Extensive research has been conducted for several years into the production and development of powerful PDE4 inhibitors. This is found to be difficult due to the fact that many potential PDE4 inhibitors are not devoid of activity on the phosphodiesterases of other families.

At the present time, the lack of selectivity of PDE4 inhibitors thus represents a major problem, given the extent of the functions regulated by cAMP. There is thus a need for powerful and selective PDE4 inhibitors, i.e. inhibitors which have no action with respect to PDEs belonging to other families and particularly PDEs which regulate cGMP.

SUMMARY OF THE INVENTION

The present invention relates to compounds of formula (I) :



(I)

- R_1 represents a group selected from hydrogen atom, methyl, methoxy, hydroxy, amino, dimethylamino, acetamido, pyrrolidin-1-yl, and hydroxymethyl;
- R_2 represent a group selected from phenyl, pyridyl, pyrimidyl, quinolyl, isoquinolyl, indolyl, pyrolyl, [1,2,3]-triazolyl, benzo[c]isoxazolyl, thienyl, pyrazolyl, isothiazolyl, imidazolyl, benzofuranyl, pyrazolo[5,1-*c*][1,2,4]triazyl each of these groups being optionally substituted from 1 to 3 groups, identical or different independently of each other, selected from halogen, trifluoromethyl, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, hydroxy, amino, acetamido, tert-butyloxycarbonylamino, cycloalkylcarbonylamino, sulfonamide, nitro, acetylmethoxy, cyclopentyloxy ;

and optionally, their optical isomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

According to a first preferred embodiment of the invention:

- R_1 represents a group selected from methyl, methoxy, amino and acetamido;
- R_2 represents a group selected from phenyl, pyridin-3-yl, and pyridin-4-yl, each of these groups being optionally substituted from 1 to 3 groups, identical or different independently of each other selected from halogen, methoxy and amino;

and optionally, their optical isomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

According to a second preferred embodiment, the invention relates to compounds of formula (I) wherein R_2 represents a pyridin-4-yl or a pyridin-3-yl group optionally substituted from 1 to 3 groups as defined in claim 1, and optionally, their optical isomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

According to a third preferred embodiment, the invention relates to compounds of formula (I) wherein R_1 represents a group selected from methoxy and amino, and R_2 represents a pyridin-3-yl group, and optionally, their optical isomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

The optical isomers, the N-oxides, as well as the addition salts with a pharmaceutically-acceptable acid or base, of the preferred compounds form an integral part of the invention.

The invention also relates to a pharmaceutical composition comprising as active ingredient an effective amount of a compound of formula (I) alone or together with one or more pharmaceutically-acceptable excipients or carriers.

The invention also relates to a method for treating a living body afflicted with a disease where the inhibition of phosphodiesterase type 4 is involved, the said method comprising the administration of an effective amount of a compound of formula (I) to a patient in need thereof.

Another embodiment of the invention concerns the use of a compound of formula (I), for the preparation of a medicinal product intended for treating a disease involving therapy by inhibition of phosphodiesterase, and more particularly of type-4 phosphodiesterase.

The compounds of the invention can be used in the treatment of complaints including cancer, acquired immunodeficiency syndrome, fibrosis, excessive scarring including excessive dermal scarring such as normal or abnormal dermal scarring following wounding

or surgery, osteoarthritis, osteoporosis, multiple sclerosis, anxiety, depression, atopic dermatitis, rheumatoid arthritis, septic shock, immune diseases including disseminated lupus erythematous, psoriasis, graft rejection and allergic rhinitis, as well as diseases involving the production of TNFα and more particularly in the treatment of inflammatory complaints such as asthma, chronic obstructive bronchopneumopathy (COPD), post-ischaemic lesions, pulmonary hypertension, congestive cardiac insufficiency, acute respiratory distress syndrome, and chronic inflammatory diseases of the intestine (IBD) such as Crohn's disease and ulcerative colitis.

DETAILED DESCRIPTION OF THE INVENTION

The compounds provided by this invention are those defined in formula (I). In formula (I), it is understood that :

- a (C_1-C_4)alkyl group denotes a linear or branched group containing from 1 to 4 carbon atoms ; examples of such groups, without implying any limitation are methyl, ethyl, propyl, isopropyl, tert-butyl,
- a (C_1-C_4)alkoxy group means the alkyl group as mentioned above bound through an oxygen atom ; examples of such compounds without implying any limitation are methoxy, ethoxy, *n*-propyloxy, *tert*-butyloxy,
- a halogen atom means fluoro, chloro, bromo or iodo,
- optical isomers refer to racemates, enantiomers and diastereoisomers.

Pharmaceutically acceptable salts of the compounds of formula I include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate,

nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Pharmaceutically acceptable salts of compounds of formula I may be prepared by one or more of three methods:

(i) by reacting the compound of formula I with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula I or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of formula I to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of

the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288, by Haleblian (August 1975).

Hereinafter all references to compounds of formula I include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The compounds of the invention include compounds of formula I as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula I.

As indicated, so-called 'pro-drugs' of the compounds of formula I are also within the scope of the invention. Thus certain derivatives of compounds of formula I which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula I having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula I with certain moieties

known to those skilled in the art as 'pro-moieties' as described, for example, in Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include

(i) where the compound of formula I contains a carboxylic acid functionality (-COOH), an ester thereof, for example, a compound wherein the hydrogen of the carboxylic acid functionality of the compound of formula (I) is replaced by (C_1-C_8)alkyl;

(ii) where the compound of formula I contains an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen of the alcohol functionality of the compound of formula I is replaced by (C_1-C_6)alkanoyloxymethyl; and

(iii) where the compound of formula I contains a primary or secondary amino functionality (-NH_2 or -NHR where R $\neq$H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of formula I is/are replaced by (C_1-C_{10})alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Moreover, certain compounds of formula I may themselves act as prodrugs of other compounds of formula I.

Also included within the scope of the invention are metabolites of compounds of formula I, that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include

(i) where the compound of formula I contains a methyl group, an hydroxymethyl derivative thereof (-CH_3 -> -CH_2OH):

(ii) where the compound of formula I contains an alkoxy group, an hydroxy derivative thereof (-OR -> -OH);

(iii) where the compound of formula I contains a tertiary amino group, a secondary amino derivative thereof ($-NR^1R^2$ -> $-NHR^1$ or $-NHR^2$);

(iv) where the compound of formula I contains a secondary amino group, a primary derivative thereof ($-NHR^1$ -> $-NH_2$);

(v) where the compound of formula I contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH); and

(vi) where the compound of formula I contains an amide group, a carboxylic acid derivative thereof ($-CONH_2$ -> COOH).

Compounds of formula I containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula I contains an alkenyl or alkenylene group, geometric *cis/trans* (or Z/E) isomers are possible. Where structural isomers are interconvertible *via* a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula I containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula I, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, *d*-lactate or *l*-lysine, or racemic, for example, *dl*-tartrate or *dl*-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula I contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.
Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, Stereochemistry of Organic Compounds by E. L. Eliel and S. H. Wilen (Wiley, New York, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula I wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such

as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula I, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

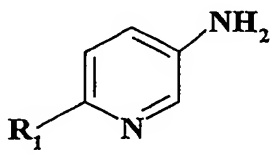
Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula I can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

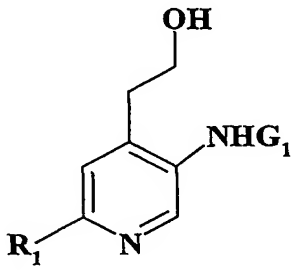
The invention also relates to a process for the preparation of compounds of formula (I), which uses as starting material a compound of formula (II):



(II)

in which R_1 is as defined in the compound of general formula (I),

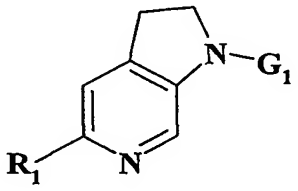
compound of formula (II) in which the primary amino group is protected in a first step by a usual protective group (G_1) used classically in organic synthesis, then is treated with oxirane or bromoethanol, in presence of a strong base to yield the compound of formula (III):



(III)

in which R_1 and G_1 are as defined hereinbefore,

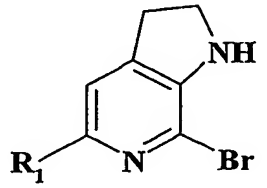
compound of formula (III) which is reacted with methanesulfonyl chloride to yield the corresponding mesylate intermediate (in the place of the primary alcohol), which is treated directly in polar condition with LiHMDS to yield to the cyclized compound of formula (IV):



(IV)

in which R_1 and G_1 are as defined hereinbefore,

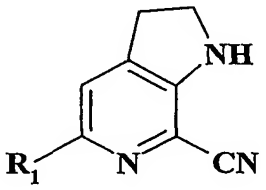
compound of formula (IV) which is treated with hydrogen bromide in the presence of hydrogen peroxide to yield to the corresponding 7-bromo-pyrrolo[2,3-*c*]pyridin of formula (V):



(V)

in which R_1 is as defined hereinbefore,

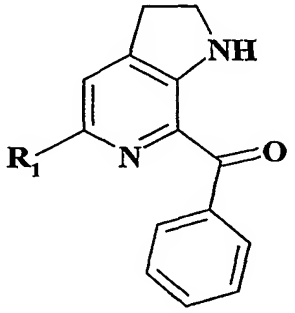
compound of formula (V), which is reacted with zinc cyanide under palladium condition or with cupper cyanide under heating or micro-wave conditions to yield to the corresponding cyanide compound of formula (VI):



(VI)

in which R_1 is as defined hereinbefore,

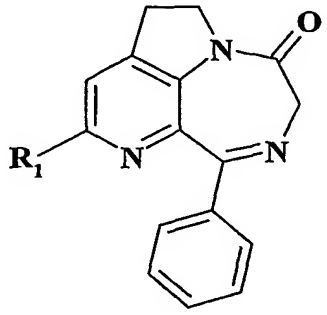
which compound of formula (VI) being treated with phenylmagnesium bromide under polar solvent to yield to the compound of formula (VII):



(VII)

in which R_1 is as defined hereinbefore,

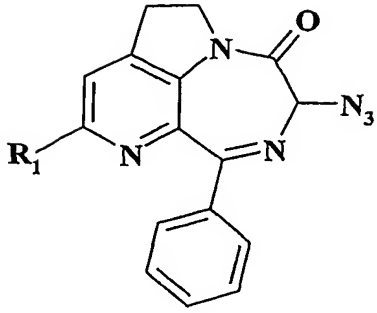
compound of formula (VII) being condensed with methyl glycinate hydrochloride in presence of pyridine, to yield to the compound of formula (VIII):



(VIII)

in which R_1 is as defined hereinbefore,

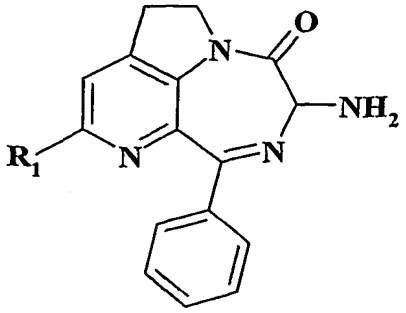
which compound of formula (VIII) is reacted with trisylazide to yield to the compound of formula (IX):



(IX)

in which R_1 is as defined hereinbefore,

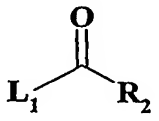
compound of formula (IX) being reduced under smooth conditions with triphenylphosphine in wet tetrahydrofurane to yield to the amino derivative of formula (X):



(X)

in which R_1 is as defined hereinbefore,

which compound of formula (X) being reacted under peptidic coupling conditions in basic medium using a classical coupling agent of organic synthesis with a compound of formula (XI):



(XI)

in which R_2 is as defined in the compounds of general formula (I) and L_1 represent a leaving group like halogen or (C_1-C_4)alkoxy,

to yield to the compound of formula (I), which is purified, where appropriate, according to a conventional purification technique, which is separated, where appropriate, into their different isomers according to a conventional separation technique, and which is

converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base.

Compounds of formulae (II) and (XI) are either commercial or obtained easily by using classical reactions of organic synthesis well known by the man skilled in the art.

Compounds of formulae (IV), (V), (VI), (VII), (VIII) and (X) described in the hereinabove process constitute intermediate compounds for the synthesis of the final products of formula (I). These compounds of formula (IV), except 1-(2,3-dihydro-pyrrolo[2,3-*c*]pyridin-1-yl)acetate and *tert*-butyl 1-(2,3-dihydro-pyrrolo[2,3-*c*]pyridin-1-yl)carboxylate, and of formulae (V), (VI), (VII), (VIII) and (X) represent new compounds useful as intermediates.

The compounds of formula (I) are purified, where appropriate, according to a conventional purification technique, and separated, where appropriate, into their different isomers according to a conventional separation technique, and converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base.

Generally, isomers of the compounds of the invention are understood to be optical isomers such as enantiomers and diastereoisomers. More especially, pure enantiomeric forms of the compounds of the invention may be separated by starting from mixtures of enantiomers which are reacted with a racemate-separating agent that can be released, the said agent being itself in the form of a pure enantiomer, which allows the corresponding diastereoisomers to be obtained. The diastereoisomers are then separated according to the separation techniques well known to the person skilled in the art, such as crystallization or chromatography, and the separating agent is then removed using conventional techniques of organic synthesis, resulting in a pure enantiomer.

The compounds of the invention that are present in the form of a mixture of diastereoisomers are isolated in a pure form by using conventional separation techniques such as chromatography.

As mentioned above, compounds of formula (I) of the present invention are phosphodiesterase inhibitors, and more particularly inhibitors of the enzyme PDE4.

In this respect, their use is recommended for the treatment of diseases or complaints involving a therapy by PDE4 inhibition. By way of example, the use of the compounds of the present invention may be recommended for the treatment of cancer, acquired immunodeficiency syndrome, fibrosis, excessive scarring including excessive dermal scarring such as normal or abnormal dermal scarring following wounding or surgery, osteoarthritis, osteoporosis, multiple sclerosis, anxiety, depression, atopic dermatitis, rheumatoid arthritis, septic shock, immune diseases including disseminated lupus erythematous, psoriasis, graft rejection and allergic rhinitis, as well as diseases involving the production of TNFα and more particularly in the treatment of inflammatory complaints such as asthma, chronic obstructive bronchopneumopathy (COPD), post-ischaemic lesions, pulmonary hypertension, congestive cardiac insufficiency, acute respiratory distress syndrome, and chronic inflammatory diseases of the intestine (IBD) such as Crohn's disease and ulcerative colitis.

In a preferred embodiment, compounds of formula (I) of the present invention are useful for the preparation of a medicinal product intended for treating a disease selected from chronic obstructive bronchopneumopathy, asthma and chronic inflammatory diseases of the intestine such as Crohn's disease and ulcerative colitis.

More particularly, the compounds of formula (I) of the present invention are useful from treating a disease selected from chronic obstructive bronchopneumopathy and asthma.

The present invention also relates to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), an isomer thereof, a N-oxide thereof, or an addition salt thereof with a pharmaceutically-acceptable acid or base, alone or in combination with one or more pharmaceutically-acceptable, inert, non-toxic excipients or carriers.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for

example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula I, a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

The compound of formula I may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20 weight % to 50 weight %, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to 88 weight % of the solutes. Alternatively, the compound of formula I may be in the form of multiparticulate beads.

The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %.

Other possible ingredients include anti-oxidants, colorants, flavourings and flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Pharmaceutical Technology On-line, 25(2), 1-14, by Verma *et al* (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula I used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(*dl*-lactic-coglycolic)acid (PGLA) microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of

the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1μg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1μl to 100μl. A typical formulation may comprise a compound of formula I, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with
the invention are typically arranged to administer a metered dose or "puff" containing from 0.001mg to 10mg of the compound of formula (1). The overall daily dose will typically be in the range 0.001mg to 40mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be

found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula I in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

The useful dosage varies according to the age and weight of the patient, the administration route, the pharmaceutical composition used, the nature and severity of the disorder and the administration of any associated treatments. The dosage ranges from 2 mg to 1 g per day in one or more administrations. The compositions are prepared by methods that are common to those skilled in the art and generally comprise 0.5% to 60% by weight of active principle (compound of formula (I)) and 40% to 99.5% by weight of pharmaceutically acceptable excipients or carriers.

For the avoidance of doubt, references herein to "treatment" include references to curative, palliative and prophylactic treatment.

The examples that follow illustrate the invention but do not limit it in any way.

The starting materials used are products that are known or that are prepared according to known operating procedures. The various preparations yield synthetic intermediates that are useful in preparation of the compounds of the invention. Some of these intermediates are novel compounds.

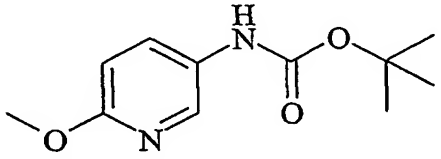
The structures of the compounds described in the Examples were determined according to the usual spectrophotometric techniques (infrared, nuclear magnetic resonance, mass spectrometry, ...)

In the experimental part:

- BOC_2O means di-*tert*-butyl dicarbonate
- TMEDA means *N,N,N',N'*-tetramethylethylenediamine
- LiHMDS means lithium hexamethyldisilazane
- DMF means dimethylformamide
- THF means tetrahydrofurane

Example 1: *N*-(4-Methoxy-9-oxo-6-phenyl-1,2,8,9-tetrahydro-5,7,9a-triaza-benzo[*cd*]azulen-8-yl)-nicotinamide

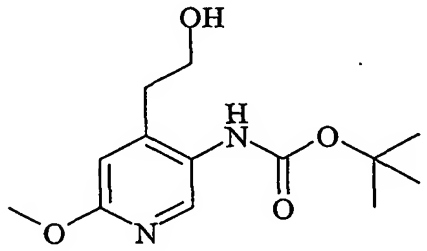
Step 1: *tert*-Butyl *N*-(6-methoxy-pyridin-3-yl)-carbamate



To a solution of 5-amino-2-methoxypyridine (25 g, 202 mmol) in 1,4-dioxane (300 ml) was added BOC_2O (48.4 g, 222 mmol) in one portion. The reaction mixture was heated at reflux for two hours, then concentrated in vacuum and further dissolved in dichloromethane. The organic phase was successively washed with HCl 1M, saturated $NaHCO_3$ and water, and dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (dichloromethane/acetone: 95/5) afforded 35.4 g of the title compound as a salmon solid. Yield : 79%.

1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, 1H), 7.80 (br s, 1H) , 6.71 (d, 1H), 6.39 (br s, 1H), 3.90 (s, 3H), 1.50 (s, 9H).

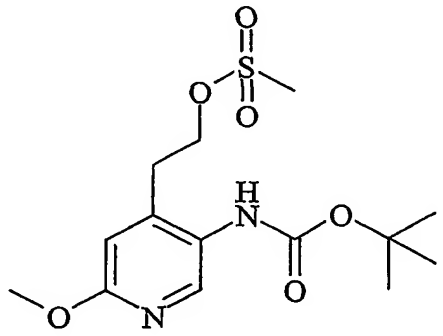
Step 2: ***tert*-Butyl *N* [4-(2-hydroxy-ethyl)-6-methoxy-pyridin-3-yl]carbamate**



To a solution of the compound obtained in step 1 (17.5 g, 78 mmol) in dry diethyl ether (400 ml) under nitrogen atmosphere was added TMEDA (28.1 g, 242 mmol) in one portion. The reaction mixture was cooled to -78°C and *n*-butyl lithium (2.5 M solution in hexane, 100 ml, 234 mmol) was added maintaining a temperature less than -65°C. The reaction mixture was warmed to -10°C and held at this temperature for one hour (the mixture is milky), re-cooled to -78°C and ethylene oxide (8.4 g, 117 mmol) was added. The reaction mixture was allowed to warm slowly to 10°C and stirred until the solution turned to transparency. The reaction mixture was quenched with iced saturated NH_4Cl, diluted with ethyl acetate. The organic phase was separated and the aqueous phase extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* to yield the crude product as a brown oil. The crude material was purified by flash chromatography (cyclohexane/ethyl acetate 70/30 then 50/50) to yield the title compound as a yellow crystallizing oil (12.8 g, 61%).

^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (br s, 1H), 7.48 (br s, 1H), 6.54 (s, 1H), 3.85 (s, 3H), 3.82 (t, 2H, 5.55 Hz), 2.74 (t, 2H, 5.56H), 1.47 (s, 9H).

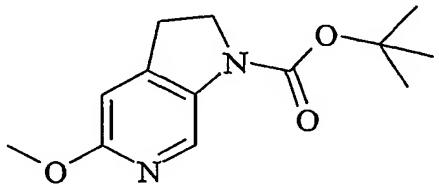
Step 3: **2{5-[(*tert*-Butylcarbonyl)amino]-2-methoxypyridin-4-yl}ethylmethane sulphonate**



To a cooled solution of the compound obtained in step 2 (12.8 g, 48 mmol) in dry dichloromethane (200 ml) under nitrogen atmosphere was added at 0°C triethylamine (14.6 ml, 105 mmol) in one portion. To this mixture, methanesulphonyl chloride (6 g, 53 mmol) was added slowly keeping the temperature below 0°C. The reaction mixture was allowed to warm to ambient temperature and stirred 1h. The reaction mixture was quenched with saturated sodium bicarbonate (3 x 50 ml). The organic phase was separated and washed with water (20 ml). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to yield the title compound as beige solid (15.6 g, 94 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 6.65 (s, 1H), 6.19 (br s, 1H), 4.46 (t, 2H), 3.9 (s, 3H), 3.01 (t, 2H), 2.97 (s, 3H), 1.49 (s, 9H).

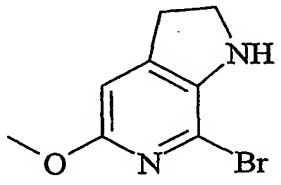
Step 4: *tert*-Butyl 5-methoxy-2,3-dihydro-pyrrolo[2,3-*c*]pyridine-1-carboxylate



To a cooled solution of compound obtained in step 3 (15.6 g, 45 mmol) in tetrahydrofuran (220 ml) was added under nitrogen atmosphere at -78°C LiHMDS (1M solution in THF, 50 ml) maintaining a temperature less than -65°C. The reaction mixture was allowed to warm slowly to ambient temperature and stirred until complete. The reaction mixture was quenched in iced water and extracted with ether. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting solid was triturated in ether to yield the title compound as a white solid (8.9 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (2br s, 1H), 6.58 (s, 1H), 4.01 (t, 2H), 3.90 (s, 3H), 3.05 (t, 2H), 1.52 (s, 9H).

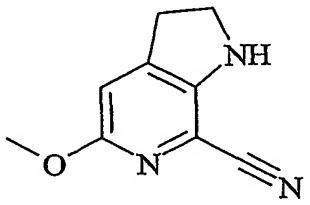
Step 5: 7-Bromo-5-methoxy-2,3-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine



To a cooled solution of compound obtained in step 4 (11.7 g, 47 mmol) in hydrogen bromide 47% W/W (27 ml, 234 mmol) was added at 10°C *via* a dropping funnel a solution of hydrogen peroxide 50% W/W (3.5 ml, 61 mmol) diluted in 8 ml of water keeping the temperature less than 30°C. The reaction mixture was stirred at room temperature until complete by TLC. The reaction mixture was cooled to less than 10°C and basified to pH 7-8 with a solution of NaOH 1M. The organic phase was separated and the aqueous phase extracted with dichloromethane. The combined extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (dichloromethane/ethyl acetate: 99/01) to yield the title compound as a yellow oil (11.9 g 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (s, 1H), 3.85 (s, 3H), 3.61 (t, 2H, 8.1 Hz), 3.10 (t, 2H, 8.1 Hz).

Step 6: 5-Methoxy-2,3-dihydro-1*H*-pyrrolo[2,3-*c*]pyridine-7-carbonitrile

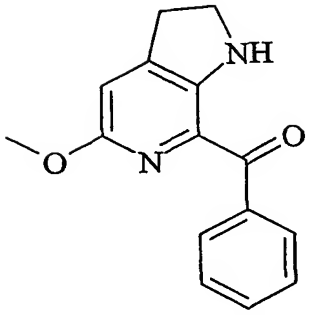


To a solution of compound obtained in step 5 (12 g, 52 mmol) in degassed DMF (100ml) under an atmosphere of nitrogen were added dppf (0.35 g, 0.64 mmol) and $Pd(dba)_3$ (0.500 g, 0.54 mmol) in one portion, followed by $ZnCN_2$ (3.66 g, 32 mmol). The reaction mixture was heated 3 hours to 130°C and stirred until complete by TLC. DMF was removed *in vacuum* and the residue was dissolved in ethyl acetate and ammoniac 14%. The organic phase was separated and the aqueous extracted with ethyl acetate. The combined organic fractions were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (dichloromethane/ethyl acetate: 98/02) to yield the title compound as a beige solid (6.4 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 1H), 4.25 (br s, 1H), 3.88 (s, 3H), 3.72 (t, 2H), 3.10 (t, 2H).

Step 7: 5-Methoxy-2,3-dihydro-1*H*-pyrrolo-[2,3-*c*]pyridin-7-yl)-phenyl

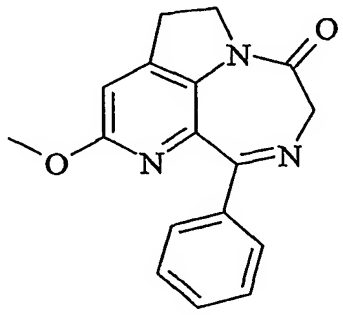
methanone



To a cooled solution of compound obtained in step 6 (0.5 g, 2.85 mmol) in THF (15 ml) under nitrogen atmosphere was added slowly at -5°C phenylmagnesium bromide (1M solution in THF, 15 ml) and stirred at this temperature for 15 minutes then warmed to room temperature until complete by TLC. The reaction mixture was quenched with a solution of ammonium chloride 1M and diluted with ethyl acetate. The reaction mixture was acidified to pH 1 using an aqueous solution of HCl 1M and the organic phase was separated. The aqueous phase was extracted with ethyl acetate. The combined organic fractions were dried over Na_2SO_4 and concentrated to dryness *in vacuum*. The crude material was purified by column chromatography (dichloromethane) to yield the title compound as a bright yellow solid (0.4 g, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, 2H, 6.6 Hz), 7.42-7.51 (m, 3H), 7.06 (br s, 1H), 6.69 (s, 1H), 3.61 (m, 5H), 3.09 (t, 2H, 9.1 Hz).

Step 8: 4-Methoxy-6-phenyl-1,2-dihydro-8*H*-5,7,9a-triaza-benzo[*cd*]azulen-9-one

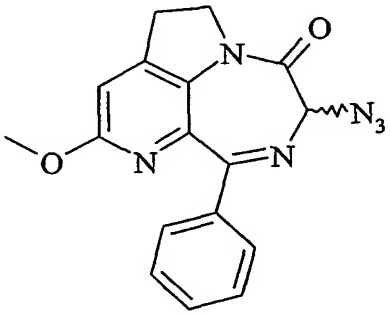


To a solution of compound obtained in step 7 (0.1 g, 0.40 mmol) in pyridine (25ml) was added methyl glycinate hydrochloride (0.054 g, 0.43 mmol). The mixture was heated two days at reflux (115°C) using a Dean Stark apparatus until complete by TLC. The reaction

mixture was concentrated to dryness *in vacuo* and diluted in dichloromethane and washed with Na_2CO_3 2.5%. The combined organic fractions were dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The crude material was purified by column chromatography (dichloromethane/ethyl acetate: 80:20) to yield the title compound as a beige solid (0.050 g, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 2H, 7.1 Hz), 7.35-7.42 (m, 3H), 6.82 (s, 1H), 4.44 (s, 2H), 4.27 (t, 2H, 7.6 Hz), 3.78 (s, 3H), 3.19 (t, 2H, 7.6 Hz).

Step 9: 8-Azido-4-methoxy-6-phenyl-1,2-dihydro-8*H*-5,7,9a-triaza-benzo[*cd*]azulen-9-one

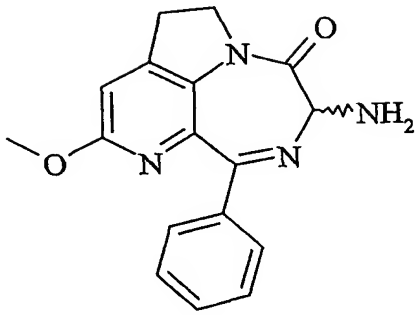


To a cooled suspension of potassium *tert*-butylate (0.042 g, 0.375 mmol) in THF (1 ml) was added at -78°C under nitrogen atmosphere, a solution of compound obtained in step 8 (0.1 g, 0.34 mmol) in THF (1 ml) dropwise. The reaction mixture turned dark blue. A solution of trisylazide (0.116 g, 0.375 mmol) in THF (1 ml) was added and the reaction mixture turned orange. The reaction mixture was stirred at -78°C for 5 minutes before glacial acetic acid was added (0.09 ml, 1.57 mmol) and allowed to warm to room temperature. The reaction mixture was diluted with dichloromethane and washed with a solution of $NaHCO_3$, water and brine. The combined organic fractions were dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The crude material was purified by column chromatography (dichloromethane/ethyl acetate: 98:02) to yield the title compound as a solid (0.3 g, 26%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.115 (m, 1H), 3.30 (m, 1H), 3.80 (s, 3H), 4.00 (m, 2H), 6.89 (s, 1H), 7.38-7.50 (m, 3H), 7.80 (d, 2H).

Step 10: 8-Amino-4-methoxy-6-phenyl-1,2-dihydro-8*H*-5,7,9a-triaza-

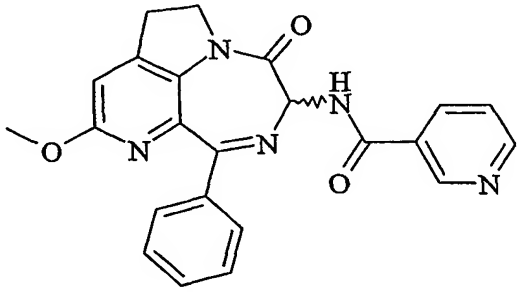
benzo[*cd*]azulen-9-one



To a solution of compound obtained in step 9 (0.14 g, 0.42 mmol) in THF (3 ml) was added triphenylphosphine (0.22 g, 0.84) and water (0.33 ml). The reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was concentrated to dryness *in vacuo*. The residue was diluted with ethyl acetate and extracted with a solution of HCl 1M and twice with water. The aqueous phase was basified to pH 12 with a solution of NaOH 1M and extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated to dryness *in vacuo* to yield the title compound as a solid (0.090 g, 69%), which was used in next step without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (br s, 2H), 3.12 (m, 1H), 3.30 (m, 1H), 3.79 (s, 3H), 3.97 (m, 1H), 4.59 (s, 1H), 4.71 (m, 1H), 6.85 (s, 1H), 7.39-7.50 (m, 3H), 7.70 (d, 2H).

Step 11: ***N*-(4-Methoxy-9-oxo-6-phenyl-1,2,8,9-tetrahydro-5,7,9a-triaza-benzo[*cd*]azulen-8-yl)-nicotinamide**



To a solution of compound obtained in step 10 (0.070 g, 0.23 mmol), in dichloromethane (3 ml) was added nicotinic acid (0.030 g, 0.24 mmol) and *O*-[(ethoxycarbonyl)cyanomethyleneamino]-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TOTU) (0.075 g, 0.23 mmol) in one portion. The reaction mixture was cooled to 0-5°C and diisopropylethylamine (0.060 g, 0.46 mmol) was added dropwise. The yellow solution

was stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane and washed with water, a solution of $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and concentrated to dryness *in vacuo*. The crude material was purified by column chromatography (dichloromethane/methanol 100/0, then 98/02 and 97/03) to yield to the desired product, which was triturated in a mixture of ether and pentane (0.080 g, 84%). Both enantiomers were separated by chiral preparative HPLC (column Chiralcel® OD-H 20x250 mm, 5µm, 17 ml/min, acetonitrile 100%). Rt = 5.79 min and 8.15 min.

^1H NMR (500 MHz, DMSO) δ 3.17 (m, 1H), 3.37 (m, 1H), 3.75 (s, 3H), 3.96 (m, 1H), 4.47 (m, 1H), 5.60 (d, 1H), 7.15 (s, 1H), 7.43 (m, 2H), 7.49 (m, 1H), 7.56 (m, 1H), 7.68 (d, 2H), 8.39 (m, 1H), 8.76 (d, 1H), 9.18 (s, 1H), 9.96 (d, 1H).

Evaluation of the *in vitro* activity of the compounds of the examples

The capacity of the compounds of formula (I) of the invention to inhibit cyclic nucleotide phosphodiesterases is evaluated by measuring their IC_{50} (concentration needed to inhibit 50% of the enzymatic activity). In the case of PDE4 enzymes, this value is compared to the IC_{50} value for rolipram, a reference inhibitor for PDE4 enzymes.

The type 4 phosphodiesterases are obtained from a cytosolic preparation extracted from a cell line of human origin, U937, according to the method adapted from T. J. Torphy et al., 1992, J. Pharm. Exp. Ther. 263: 1195-1205.

The other types of phosphodiesterases are obtained during a partial purification by FPLC on a Mono Q column (anion exchange column) according to a method adapted from Lavan B. E., Lakey T., Houslay M. D. Biochemical Pharmacology, 1989, 38(22), 4123-4136, and Silver P.J et al., 1988, Eur. J. Pharmacol. 150: 85-94, either starting with cell lines of human origin for PDE1 (monocyte line TPH1) and PDE5 (line derived from an adenocarcinoma MCF7), or starting with dog aorta for PDE3, or, for human PDE3A, starting with a cloning of genes in SF21 insect cells into baculovirus, according to the method adapted from Luckow, V. A. et al., 1991 in Recombinant DNA Technology & Applications., eds. Prokop, Bajpai, R. K. & Ho, C.S., pp 97-152.

The measurement of the enzymatic activity for the various types of PDE, and in particular the PDE4 enzymes, is carried out according to a method adapted from W. J. Thomson et al. 1979, Advances in Cyclic Nucleotide Research, Vol. 10: 69-92, ed. G. Brooker et al. Raven Press, NY.

For the determination of the IC_{50} value, the enzymatic activity is measured in the presence of the inhibitor in a concentration range from 0.1 to 100 μM.

Using this test, the racemate of compound of Example 1, the first enantiomer (Rt=5.79 min) of compound of Example 1, and the second enantiomer (Rt = 8.15 min) of compound of Example 1 show respectively an IC_{50} at 6.1 μM, 4.3 μM, and 73 μM.